

REMARKS

Reconsideration of this Application and entry of these Amendments is respectfully requested. By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which they are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

No new matter has been added as a result of the present amendments.

In the claims

Claims 1-3, 5-16, 18-20, and 29 are pending in this application.

Claims 1, 9, and 16 have been amended to further clarify the claimed subject matter. Support for these amendments can be found throughout the claims as filed.

35 U.S.C. §103 Rejections

1) The Office Action rejects claims 1-3, 10-16, 19-20, and 29 under 35 U.S.C. §103(a) as being unpatentable over Schim (Current Medical Research and Opinion, Vol. 20, No. 1, January 2001, p. 49-53; "Schim") in view of Johnson *et al.* (USP 5,512,547; "Johnson") in view of Cephalalgia, An International Journal of Headache, Volume 24, Supplement 1, 2004 ("Cephalalgia") in view of Aoki *et al.* (USP 6,896,886; "Aoki"). Applicants respectfully traverse this rejection.

Applicants traverse the rejection. Nevertheless, to expedite prosecution the rejected claims have been amended to include the limitation of claim 5 ("by intramuscular or subcutaneous administration to a location on or within a head of a patient"), which was not subject to the §103 rejection. Therefore, the rejection should be withdrawn.

2) The Office Action rejects claims 1-3, 5-16, 18-20, and 29 under 35 U.S.C. §103(a) as being unpatentable over Tepper *et al.* (Cephalalgia, 2003, 23,

581-762; "Tepper") in view of Johnson in view of Cephalalgia, 2004 and further in view of Aoki. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness under 35 U.S.C. §103, the Office must meet four conditions. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art itself would have *provided* one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). *KSR Int'l Co. v. Teleflex, Inc.*, teaches that this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). Nevertheless, the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

Tepper, a poster presentation, discusses botulinum toxin administration in the preventative treatment of refractory headaches (treatment of refractory headaches in patients that are medication overusers as well as non-overusers). Unlike the pending claims, Tepper does not suggest methods for treating patients suffering from an acute pain medication overuse disorder, where the patient experiences pain after the intake of acute pain medication. Nor does Tepper teach the use of pure botulinum toxin and further, Tepper does not teach or disclose administration according to the instantly claimed methods, providing no

administration information beyond the fact that each patient had received 100 units of botulinum toxin A.

The Office applies Johnson to remedy the absence of teaching related to pure botulinum toxin. While Johnson does appear to teach pure toxin, the reference does not at any point state that the pure toxin is pharmacologically equivalent to the toxin complex used in Tepper. The Office's citing of the supposed advantages displayed by the toxin vice the complex are irrelevant in light of this; possible advantages in shelf life and immunogenicity are of no benefit if the "new" molecule does not perform as well as the "old" molecule, and Johnson provides no indication that the pure toxin works as well as the toxin complex inside the patient. Indeed, Johnson proposes a completely new formulation as compared to the botulinum toxin type A formulation used in Tepper, one which includes trehalose, and no person of ordinary skill in the art would assume that the pure toxin, with its completely different formulation, would prove as effective pharmacologically as the toxin complex used in Tepper. This shortcoming, especially when combined with Tepper's absolute lack of guidance regarding administration techniques and locations, prevents these references from rendering the pending claims obvious. Further, Johnson teaches nothing relating to headaches, or indeed to non-muscle-related effects of toxin administration, as it measures toxin activity solely utilizing a muscle paralysis lethality assay. Clearly, as seen in Figures 1 through 5, compositions of the present invention achieve significant success in reducing both headache frequency and medication ingestion, symptoms distantly related at best to muscle paralysis.

In addition, a long line of case decisions (the "*Papesch*" doctrine) has established that "evidence of unobvious or unexpected advantages or advantageous properties may rebut a prima facie case of obviousness based on structural similarities." *In re Chupp*, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) citing *In re Papesch*, 137 USPQ 43, 48 (CCPA 1963). Such unexpected advantages or advantageous properties include the properties demonstrated by the comparison of Tepper and Figures 1-5 of the present application. Figure 1 of Tepper displays

the headache frequency of two groups of patients following treatment with botulinum toxin. The figure clearly shows that between medication overusers and medication non-overusers, the non-overusers had a higher headache frequency at baseline. The figure also shows that following the botulinum treatment, the headache frequency of the non-overusers decreased more than that of the medication overusers and also that the frequency at baseline plus 3 months was lower for non-overusers. Thus, Tepper shows that botulinum treatments are more effective in treating medication non-overusers as compared to overusers. Therefore, the fact that the claimed treatment methods (relating to treatment of overusers) are so effective (as demonstrated in Figures 1-5) is an unexpected advantage. Further, Tepper teaches away from using botulinum toxins to treat medication overusers, because Figure 1 of Tepper clearly shows that botulinum toxins are more effective in treating non-overusers.

Thus, Applicants assert these references cannot anticipate the pending claims, and respectfully ask that the rejection be withdrawn.

Conclusion

For the foregoing reasons, Applicants believe all the pending claims are in condition for allowance and a Notice of Allowance to that effect is respectfully requested. The Commissioner is hereby authorized to charge any additional fees which may be required for entry of this paper, or credit any overpayment, to Deposit Account No. 01-0885. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, the Examiner is kindly urged to call the undersigned at telephone number (714) 246-6458.

Respectfully submitted,

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